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THE ETIOLOGY OF ACUTE LOBAR PNEUMONIA, CONSIDERED FROM A BACTERIOLOGICAL POINT OF VIEW.

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Members of the Faculty:

I had the honor at the last Annual Meeting of this Faculty of addressing you upon the *Causation of Diphtheria*, and I endeavored then to present the results of the bacteriological study of this disease in a manner which might be helpful to the practitioner of medicine. It has seemed to me that it may be acceptable on this occasion to consider *Acute Lobar Pneumonia* from a similar point of view.

Various names have been given to the bacterium which we now believe to be the specific cause of acute lobar pneumonia, such as micrococcus Pasteuri (Sternberg), micrococcus of sputum septicæmia (A. Frænkel), diplococcus or diplobacillus or pneumococcus of Frænkel and Weichselbaum, diplococcus pneumoniæ (Weichselbaum), micrococcus or diplococcus lanceolatus capsulatus (Foà and Bordoni-Uffreduzzi), micrococcus pneumoniæ cruposæ (Sternberg). Of these names micrococcus or diplococcus lanceolatus, diplococcus pneumoniæ and pneumonia coccus or pneumococcus have gained the widest currency and will be used in this article. Perhaps the name micrococcus lanceolatus is the least objectionable. Such names as pneumococcus, micrococcus pneumoniæ cruposæ suggest an exclusive relationship of this organism to croupous pneumonia, whereas this

same organism is concerned in the causation of epidemic cerebro-spinal meningitis and many other affections independent of pneumonia.

The micrococcus lanceolatus was discovered by Sternberg in September, 1880, by inoculation of rabbits with his own saliva. It was next found by Pasteur in December, 1880, by inoculating rabbits with the saliva of a child dead of hydrophobia. Pasteur's observations were the first to be made public in January, 1881. Sternberg's first publication on this subject appeared in April, 1881.

At this time there was no suspicion that this micrococcus of the saliva is concerned in the causation of lobar pneumonia.

No little sensation was made by Friedländer's publication in November, 1883, in which he described cultures of a bacterium to which he gave the name pneumococcus. We now know that the so-called pneumococcus of Friedländer is an organism entirely distinct from the micrococcus lanceolatus and is to be regarded as a bacillus. This pneumobacillus of Friedländer is probably in no way concerned in the causation of genuine acute lobar pneumonia in man. Friedländer's method of cultivation in nutrient gelatine at ordinary temperatures precluded his obtaining the genuine pneumonia coccus. The historical importance of this publication of Friedländer, is that he was the first to describe cultures obtained from croupous pneumonia by using Koch's solid nutritive media, that his pneumobacillus was widely accepted until the year 1886 as the specific cause of croupous pneumonia and especially that his results gave an impetus to the further bacteriological study of this disease by modern methods.

For a while there was much confusion of the genuine pneumonia coccus with Friedländer's bacillus. Thus the observations of Talamon in 1883, of Salvioli in 1884 and of Sternberg in 1885, unquestionably pertained to the micrococcus lanceolatus but these writers thought they were working with the pneumococcus which had been described by Friedländer.

This period of confusion was brought to an end by the exhaustive and fundamental researches of A. Frænkel, published in 1886. His articles furnished a full and accurate description of the leading characters of the micrococcus lanceolatus, rendered probable its causal relation to acute lobar pneumonia, separated this organism clearly from the pneumobacillus of Friedländer and recognized its identity with the micrococcus of sputum septicæmia.

Not less important were the independent investigations of Weichselbaum, published in October, 1886, and based upon the study of a much larger number of cases. Foà and Bordoni-Uffreduzzi also deserve mention among the pioneer investigators of this period. In the same year they reported their observation of lanceolate diplococci in the exudate of epidemic cerebro-spinal meningitis. They identified correctly this micro-organism, which they called meningococcus, with Frænkel's pneumonia coccus.

Since these fundamental researches, each year has been rich in contributions to the literature of our subject.

As the name lanceolate coccus implies, the typical form of the pneumonia coccus is oval, with one end somewhat more tapering than the other. It is often compared in shape to the flame of a candle or to a grain of barley. Regularly oval and spherical forms, however, are not uncommon and there may be actual rods or bacilli. The propriety of calling this organism a coccus is open to question. Its typical form is transitional between a coccus and a bacillus. Usage is in favor of calling it a coccus, but some good authorities prefer to regard it as a bacillus.

The arrangement in pairs is so characteristic that this has given origin to the name diplococcus pneumoniæ. Pneumococci not infrequently appear in short chains and, especially in old cultures and when devoid of virulence, they may grow in long and curved chains, regular streptococci.

In fact, there is good reason to believe that the micrococcus lanceolatus belongs to a species presenting varieties which are represented by every transition from single and double cocci to long streptococci and which are endowed

with varying degrees of virulence and that some of these varieties are almost constantly present in the mouth. This relation of the pneumococcus, which ordinarily in croupous pneumonia appears as a diplococcus, to streptococci is of much interest in view of the increasing importance attached to primary and especially secondary streptococcus infections. I shall have occasion throughout this article repeatedly to refer to the extraordinarily variable characters of the pneumonia coccus, which render a concise and accurate description of the organism difficult.

The third morphological characteristic of the pneumonia coccus is the presence around it of a clear gelatinous capsule which can be stained with various aniline dyes. The combination of the three traits mentioned suggested the descriptive name diplococcus lanceolatus capsulatus. Capsules are as a rule readily demonstrable only around the cocci growing in the animal body, although they may be present also in cultures.

Degenerating and dead pneumococci, which are very common in old inflammatory exudates caused by this organism, often leave behind them empty or faintly staining capsules.

The micrococcus lanceolatus is not motile. It never forms spores. It stains well with Gram's and Weigert's fibrin stain.

It grows best at temperatures approaching that of the human body. Below 24° C. (75° F.) the growth may cease, but sometimes there is development at as low a temperature as 18° C. (64.4° F.), especially when the organism has been cultivated for some time outside of the body and has lost virulence. Nutrient gelatine, therefore, which melts at 22°-24° C., is not a medium adapted for obtaining first cultures of the pneumococcus, and as already mentioned it was doubtless in consequence of the use of this medium that Friedländer failed to isolate the genuine micrococcus of croupous pneumonia.

The pneumococcus is capable of growing on all of our ordinary culture media but there is no other known organism which will grow on so many media and at the same time

is so particular as to the exact composition of the medium. Slight differences in the reaction of the medium, in the quality of the peptone or of the meat used to prepare the medium often determine whether or not growth takes place.

The most suitable and generally employed culture medium for this organism is feebly alkaline nutrient agar or a mixture of agar and gelatine. The growth is usually delicate and grayish in color, but it may be more abundant and opaque. Gelatine is not liquefied. Milk is usually soured and coagulated. No visible growth on potato usually appears. The culture in bouillon may be diffusely cloudy or in the form of a granular sediment. Growth occurs without as well as with the presence of free oxygen.

The variability in the properties of this coccus is manifested not less in its behavior in culture media than in other respects. Decided modifications in cultural characters, particularly as to luxuriance of growth and capacity of development at low temperatures can often be brought about by artificial cultivation. Abundant growth at low temperatures is generally associated with loss of virulence and is often observed in late generations of artificial cultures of primarily virulent pneumococci.

One of the most striking properties of the lanceolate coccus both in the animal body and especially in cultures is its short viability, a property, however, which like most of the others is not without exceptions. The maximum development in cultures at body temperature is attained in twenty-four hours or less. After this there is usually progressive and rapid death of the bacteria so that at the end of four to seven days the cultures are usually dead. Cultures capable of surviving two weeks or more are generally not virulent, but to this rule there are exceptions.

In order to be sure of keeping the cultures alive they should be planted over every day or two. But even this care will not as a rule preserve the virulence of the organism.

After the third or fourth generation it is not uncommon to find marked diminution of virulence and after ten generations, and often sooner, virulence has generally nearly or

entirely disappeared. To keep up the virulence of the organism the plan is usually adopted of transmitting it frequently through rabbits, but even this will not always succeed.

This short viability and rapid loss of virulence give to the micrococcus lanceolatus a quite exceptional position among pathogenic bacteria and they constitute an annoying obstacle to systematic experiments with this organism.

The limited duration of life of the lanceolate coccus is a matter of great practical interest. It is capable of longer life in the virulent state in susceptible animals and in human beings than in artificial cultures but it is apt to die even in the living body sooner than most other pathogenic bacteria. Dead pneumococci are found often in large number in empyæmas and in the exudate of croupous pneumonia. This short vitality is doubtless one reason why empyæmas and other local inflammations caused by the lanceolate coccus usually afford a more favorable prognosis than those caused by the longer lived streptococcus pyogenes and why a single aspiration of a pneumococcus empyæma may be followed by a permanent cure. But here as well as with other properties of this peculiar micro-organism it is necessary to keep in mind the frequent exceptions to the rule, instances occurring in which virulent pneumococci are found in empyæmas and other inflammatory exudates at least six months old.

The pneumococcus may suffer a progressive loss of virulence during the course of croupous pneumonia so that at the end of the disease the cocci may be nearly devoid of virulence, but this behavior is not sufficiently constant to establish a rule.

Pneumonia cocci in blood and sputum are in general tolerably resistant to drying, living and retaining their virulence in the dried state sometimes for at least four months, although they may die much sooner. This resistance to desiccation as well as other reasons indicate the propriety of destroying or disinfecting pneumonic sputa.

According to Sternberg the pneumonia coccus is killed by exposure for ten minutes to a temperature of 52° C. (125.6°

F.). The action of sunlight is injurious to this as well as to other bacteria.

Experiments upon animals and observations on human beings prove that the micrococcus lanceolatus is an organism of the most manifold and varied pathogenic possibilities. It is the cause in human beings of a large number of affections formerly regarded as etiologically distinct. Before considering these it is desirable to say something concerning the results obtained by inoculation of animals.

We meet under natural conditions and we can readily obtain by artificial cultivation pneumococci totally devoid of any virulence to animals and at the other extreme we find pneumococci capable of killing rabbits by septicæmia in eighteen hours or less. Between these extremes occur pneumococci of all possible degrees of virulence and capable of causing manifold pathological lesions.

The experimental results vary with the animal, with the number and virulence of the bacteria inoculated and with the site of the inoculation. Rabbits and mice are the most susceptible animals. The principal symptoms which may be observed in rabbits inoculated with virulent pneumococci are fever, diarrhœa, albuminuria and shortly before death convulsive seizures. Pulmonary œdema sometimes accompanies the death agony.

Septicæmia with multiplication of the cocci in the blood is regarded as the leading type of experimental pneumococcus infection of rabbits. With this the rabbit usually dies in one to three or four days. The more common and important lesions are serous, fibrinous or fibrino-purulent exudation around the point of inoculation if this has been subcutaneous, swelling of the spleen, which may be either hard or soft, small, opaque foci of necrosis in the liver, fatty degeneration of the heart, ecchymoses, and sometimes hyaline thrombi in the renal capillaries. Sometimes there is fibrinous inflammation of the peritoneum or other serous membrane. Cocci are usually abundant in the blood but they may be scanty. They are always numerous in recent local exudates.

The attempt has been made to establish distinct biological varieties of the micrococcus lanceolatus on the basis of diverse pathological effects in these septicæmias, especially on the basis of the consistence of the spleen and the character of the exudate at the point of inoculation. But these alleged distinctive characters have not been found to be sufficiently constant to justify a sharp separation into distinct varieties.

A second type of pneumococcus infection in rabbits, not sharply separated from the septicæmic type, is that characterized by spreading, localized, usually multiple fibrino-purulent inflammation without many cocci in the blood. There is evidence that this exudative type depends upon weakened virulence of the cocci. Rabbits affected with this form of the disease live usually four to fifteen days and sometimes longer. Very virulent pneumococci may produce this exudative type in rabbits rendered partly immune from infection. In the majority of cases there are associated with extensive subcutaneous exudation spreading from the site of inoculation, similar fibrino-purulent inflammation of one or more serous membranes and sometimes hepatized pulmonary areas. The spleen is often little or not at all changed. Cocci are usually few in the blood but in enormous numbers in the exudates, in which in the course of time many degenerate and die. The animal becomes emaciated and anæmic, commonly with marked leucocytosis.

Croupous pneumonia in human beings belongs to the exudative rather than to the septicæmic type of pneumococcus infection. Inasmuch as the occurrence of such spreading inflammations with little invasion of the blood by pneumococci is experimentally shown to depend chiefly upon the relation existing between the virulence of the coccus and the resistance of the animal and as we cannot suppose that the pneumococci which cause croupous pneumonia are of weakened virulence, the inference seems warranted that man ranks among those relatively insusceptible to this organism.

A third type of disease caused by subcutaneous inoculation of the diplococcus pneumoniæ is the formation of an

abscess at the point of inoculation. This occurrence indicates either still less virulence than in the preceding types or, with the same virulence, greater resistance on the part of the animal. Rabbits which have been rendered sufficiently immune to be protected from septicæmia often acquire a local abscess at the point of inoculation. Under these conditions the micrococcus lanceolatus is an exquisitely pyogenic micro-organism, as it may also be in man. Usually the animal recovers after evacuation of the abscess.

A rare form of experimental pneumococcus disease is pyæmia, with multiple suppurative foci in the joints and other parts of the body.

It is noteworthy that in animals as well as in man the micrococcus lanceolatus is capable of producing not only fibrinous but also genuinely purulent inflammations of the serous membranes.

The efforts to reproduce in animals a form of pneumonia in all respects identical with acute lobar pneumonia as it occurs in man have been only moderately successful. To accomplish this it is evident that the animal must not die of quick septicæmia. Hence these experiments have been made either with virulent cultures on relatively insusceptible animals such as the dog, or with attenuated cultures on rabbits. A few experimenters claim to have produced by intrapulmonary or tracheal inoculations typical lobar fibrinous pneumonias, but the usual result if the organism is sufficiently virulent, is the production of pleurisy and pericarditis with or without circumscribed areas of pulmonary hepatization.

So far as known the domestic animals are not subject to a form of pneumonia etiologically and anatomically identical with croupous pneumonia of man. We do not usually in our experimental tests with pathogenic micro-organisms on animals reproduce the exact counterparts of human diseases nor is it necessary or to be expected that we should do so in order to rest satisfied with our experimental evidence. We possess conclusive experimental proof that the pneumococcus is capable of producing spreading inflammatory exudates

with all of the histological and bacteriological characters of the exudate in croupous pneumonia as it occurs in man.

As the micrococcus lanceolatus is the cause of many cases of cerebro-spinal meningitis, (hence the synonym, meningococcus) the attempt has been made by submeningeal inoculation to reproduce this lesion in animals and with occasional success.

Endocarditis which is a very rare result of simple subcutaneous or intravenous inoculation of the pneumococcus can be readily produced by the well known method adapted to cause infectious endocarditis, viz.: by first injuring the valves by means of a sterilized probe passed from the carotid artery into the left ventricle and then injecting the cultures. This is an illustration of the predisposing influence to localized infection of a locus minoris resistentiæ.

Various other special localizations such as arthritis and periarthritis, ostitis and otitis media have been produced by special methods of inoculation, in order to demonstrate the possibility of reproducing in animals similar affections caused by the same organism in human beings.

It is evident from the foregoing review, which is only partial, of the pathogenic effects which may be produced by the micrococcus lanceolatus in animals that we possess a rich mass of experimental data to aid us in explaining the multiform manifestations of infection by this micro-organism in human beings. The pathogenic effects produced are a function on the one hand of the number and virulence of the infecting cocci and on the other hand of the degree of susceptibility of the individual and according to these differences the result is now septicæmia, now single or multiple sero-fibrinous or fibrinous or fibrino-purulent or purulent or hemorrhagic exudations or now a localized abscess.

The transmission of pneumococci from mother to fœtus has been demonstrated both in human beings and in animals. It is interesting to note that in the few hitherto reported observations in human beings in which the pneumococci have been demonstrated in the embryos of mothers affected with croupous pneumonia, there has been no pneumonia in

the fœtus although the organisms were present in the blood, whereas in infants congenitally infected who had lived some hours after birth, actual pneumonia has existed. Netter concludes that it is necessary that the child should have breathed in order to acquire localization of pneumococcus infection in the lung. This is an illustration, and there are others in the case of different diseases, of the difference in susceptibility between the embryo and the infant after birth.

To produce intra-uterine infection of the fœtus the pneumococci must of course have circulated in the blood of the mother and have broken through the placental barrier, which as is well known is a perfect physiological filter for inanimate particles. But living micro-organisms are capable of damaging in various ways the placental tissue and opening a passage into the fœtal vessels. Some micro-organisms do this often, others only exceptionally or not at all.

It is probable that the transmission of pneumococci from mother to fœtus is exceptional in the case of human beings. The toxic substances produced by micro-organisms, being soluble, can of course pass much more readily through the placental vessels to the fœtus than the micro-organisms themselves, and these poisons often cause the death of the fœtus. It is well known that pneumonia developing during pregnancy is likely to bring about miscarriage. The same is to be noticed in mice and rabbits inoculated with virulent pneumococci. Neither in human beings nor in animals does abortion necessarily attend pneumococcus infections.

Pneumococci have been found in the milk of rabbits inoculated with the virulent organism and suckling rabbits have been infected by the ingestion of this milk. Pneumococci have been detected also in the milk of women affected with croupous pneumonia. As to the frequency of this occurrence we have not sufficient information.

Evidence is constantly accumulating that pathogenic bacteria do injury chiefly by their toxic chemical products. It was thought at one time that the most important of these poisonous products are crystallizable alkaloidal substances called ptomaines, but it is now known that the toxic products

which produce the more characteristic and specific manifestations of an infectious disease are of an entirely different nature. These more specific poisons are believed for the most part to be proteids and are called toxalbumins or toxic proteids. We know very little of their chemical constitution and identify them chiefly by their biological effects. They have not been separated in a state of purity but are contained usually in albuminous precipitates. They are formed both in the body of the infected animal and in cultures, often more abundantly in the former. In fact with some pathogenic bacteria which give evidence of the formation of toxins in the infected body, there has been difficulty in demonstrating poisonous substances in cultures.

The most powerful toxic bacterial proteids are produced by the bacilli of diphtheria and of tetanus which multiply as a rule only or chiefly locally near the point of entrance. In the experimental septicæmic infections, such as may be caused by the pneumococcus, where there are abundant invasion and multiplication of the bacteria in the circulating blood, we do not find such concentrated and powerful poisons as in the more distinctively toxic diseases like tetanus and diphtheria.

Cultures of the pneumonia coccus as a rule do not contain in a concentrated form toxic substances. As much as thirty to forty cubic centimeters of beef broth cultures of virulent pneumococci, sterilized or deprived by filtration of bacteria, can sometimes be injected into the circulation of rabbits without grave symptoms. Cultures concentrated by evaporation at low temperature cause death when injected in smaller quantities. As might be expected with an organism so variable in all of its properties, some cultures are more poisonous than others, so that much smaller quantities than those mentioned may cause intoxication.

There is clinical evidence both for human beings and animals that the pneumococcus may produce toxic substances in the living body. In fact we find in the blood of rabbits dead of pneumococcus infection, more concentrated toxic substances than we are able to demonstrate in

cultures. The blood of human beings affected with croupous pneumonia is often highly poisonous for rabbits, three to six cubic centimeters of such blood injected into the circulation of rabbits sufficing to cause grave symptoms and even speedy death. This blood may retain its toxic properties for a time after the crisis.

With the exception of the unconfirmed observation of Bonardi no toxic ptomaines have been found in pneumococcus cultures. There have, however, been obtained from cultures and from the blood and tissue juices of animals dead of infection albuminous substances, possessing poisonous properties. It is believed therefore that the specific poison produced by the pneumococcus, as well as the poisons of most pathogenic bacteria, belong to the group of toxic albumins. It has received from the Klemperers the name pneumotoxin. The name is a convenient one but it must not be inferred that it refers to any substance which has hitherto been isolated in a state of chemical purity or which has been demonstrated to be of an albuminous nature.

Grave constitutional symptoms and some of the local lesions of pneumococcus infection are referable to the poisonous substance or substances called pneumotoxin. It is questionable, however, whether this substance is concerned in the production of local inflammatory exudates. These exudates must be caused by bacterial products possessed of powerful positive chemotactic properties, that is, of the power of attracting leucocytes. Experiments indicate that the specific toxalbumins repel rather than attract leucocytes. It is held by Buchner and others that substances called bacterio-proteins, set free from degenerating and dead bacteria, are the chief agents which manifest positive chemotactic properties. This view fits in with the fact that it is especially bacteria of weakened virulence in susceptible individuals or virulent bacteria in more resistant individuals which attract leucocytes and set up local inflammations. There is evidence however, that living and vigorous bacteria may also attract leucocytes so that we cannot accept Buchner's observations as excluding other explanations of

the accumulation of inflammatory products, more particularly leucocytes, around bacteria.

Whether we suppose that the positively chemotactic substances are derived from pneumococci already damaged by the living cells and fluids of the body in accordance with Buchner's view, or from still active and thriving pneumococci, there is good reason to believe that these substances are not identical with the toxalbumins which, by their absorption into the circulation, cause the graver constitutional symptoms often observed in croupous pneumonia and other pneumococcus infections. The variability in these clinical manifestations may depend partly on the susceptibility of the patient and partly on the virulence of the pneumococcus. Varying degrees of virulence of a micro-organism are to be interpreted usually as varying capacity to produce toxic substances.

A class of bacterial products of great importance are those which are capable of producing immunity. Rabbits can readily be rendered insusceptible to fatal doses of virulent pneumococci. All of the known principles of producing artificial immunity have been successfully employed in protecting rabbits from the micrococcus lanceolatus. These principles of immunization are:

1. Inoculation of small, not fatal, quantities of virulent cultures of the specific micro-organism causing the disease.

2. Inoculation of the specific micro-organisms partly or wholly attenuated in virulence. The ways by which virulence can be weakened or annulled are various, and consist chiefly in exposure to agencies injurious to bacteria. In the case of the pneumococcus we often meet under natural conditions the organism so weakened in virulence as to serve as a vaccine against the virulent variety.

3. Injection of products of the bacteria causing the disease, either products contained in sterilized cultures or in the germ-free filtrate of cultures or products obtained from the body of an infected individual. These substances may be used when still toxic, or better, as a rule, after diminution or removal of their toxicity by heat, mixture with chemical

antiseptics or other means. This class constitutes the so-called chemical vaccines in distinction from the living vaccines just described.

4. Injection of the blood serum or other fluids from animals artificially rendered immune from the disease. This method is different in principle from the first three, and the resulting immunity presents important peculiarities. As this immune serum possesses also curative properties, it is called curative or healing serum.

Inasmuch as it is by their chemical products that bacteria confer immunity, as well as cause disease, the distinction which appears in the preceding classification between living vaccines and chemical vaccines is not so fundamental as at first glance it might appear.

The immunizing bacterial products are believed to be proteids, and especially of the class derived from the bacterial cells, but we recognize them by their physiological properties rather than by any known chemical tests. The relation in which they stand to the toxic proteids is not definitely known. Inasmuch as the vaccinating power of sterilized or filtered cultures deprived partly of toxicity by heat or by other means is greater than that of the unaltered toxic products, it is held that the immunity-conferring products are either distinct from the toxic products or are derived from them.

When we introduce vaccinating substances, belonging to the first three methods just described, immunity does not ensue at once, but there is a period of reaction, often severe, with fever, local inflammation and other symptoms, which precedes the establishment of immunity. In the case of the pneumococcus this period of reaction lasts three or four days after intravenous injection and about two or three weeks after subcutaneous injection. The resulting immunity may be augmented by repeated successive injections of vaccines of increasing strength and finally of increasing quantities of the virulent organism. In this way rabbits may be protected against subsequent inoculation with several times the fatal dose of virulent pneumococci. Such very high degrees of

immunity as have been secured from tetanus by vaccination, have not, however, been obtained from pneumococcus infection. The immunity may last at least two years, but usually disappears sooner.

The protection which is afforded by injecting the blood serum of an animal already rendered by vaccination or by recovery from the disease immune from the pneumococcus rests upon a different principle from that afforded by vaccination with the living micro-organism or its products. By the former method we inject a fluid which is already endowed with properties upon which immunity depends, whereas by the latter methods these properties must be developed before immunity is established. In using immune serum we simply transfer a part of the immunity possessed by one animal to another, or at least we introduce substances which quickly bring about that change in the body upon which immunity depends. Hence this is called passive immunity, in distinction from the active immunity induced by vaccination. Passive immunity appears at once or within a few hours after the injection of immune serum, and is not preceded or attended by any noteworthy reaction. To compensate for this speedy and safe development, passive immunity lasts a shorter time than active immunity, and is in direct proportion to the quantity of immune serum introduced and the degree of immunity possessed by the animal from which the serum is derived. It is only a fraction of the immunity of the animal yielding the serum.

Acquired immunity is the result of a specific reaction of the living body, which in the case of the pneumococcus can be produced only by the direct or indirect products of this organism.* Hence when we find that the blood and fluids of persons recently convalescent from pneumonia is capable of protecting rabbits from infection with the pneumococcus, and that this property is absent from the blood before an attack of pneumonia, we feel justified in inferring that the pneumococcus has been operative in the causation of the pneumonia.

*To this general statement an exception must be admitted if Bonome's assertion be confirmed that rabbits may be protected from the pneumococcus by the sterile filtrate of cultures of the bacterium of rabbit septicæmia.

Different explanations of artificial immunity from pneumococcus infection have been offered. One theory is that the blood and fluids of the immune individual have acquired the power of destroying the specific poison or pneumotoxin. A second theory is that the blood and fluids exert a direct germicidal action on the pneumococci. A third theory is that the leucocytes and other cells act as phagocytes and eat up the bacteria.

The first or antitoxic theory is advocated especially by the Klemperers. According to this view immunity from pneumococcus infection depends upon the same principle as has been proven for immunity from tetanus and diphtheria. The substance in the blood and fluids which acts as a direct antidote to the specific bacterial poison is called antitoxin, in the present case anti-pneumotoxin. The Klemperers explain the crisis of pneumonia by the sudden or critical production of the antitoxin. As soon as the poisonous weapons of bacteria are destroyed, these organisms, even if they survive for a time, are reduced to the level of ordinary saprophytes, and are as incapable of doing harm as a venomous snake is after extraction of its poison fangs.

The observations upon which the Klemperers base their fascinating theory, are opposed by those of several other investigators, and we cannot by any means consider the antitoxic theory of immunity from pneumococcus infection as proven.

Nor are the results of different experimenters regarding the second and third theories in accord. As might be predicted, Metchnikoff and his students find abundant evidence for the phagocytic theory of acquired immunity from the pneumococcus as from all other infections. As with immunity from many other infectious diseases, it cannot be said that we possess at present any thoroughly demonstrated explanation of the basis of immunity from this organism.

A most important characteristic of the blood serum and some other fluids from animals or human beings who have recently acquired immunity from pneumococcus infection is

that they are capable not only of protecting a susceptible animal from subsequent inoculation with the organism, but also of protecting after such inoculation. This is the so-called healing property which, in some degree, belongs to the blood and fluids in most cases of solid acquired immunity from infectious bacteria. Protection after reception of the virus, however, is by no means so simple a matter as mere immunization before reception.

When the immune serum is introduced soon after the inoculation with the virulent organism, it must be given in larger quantity than is required a few hours before inoculation. With each succeeding hour the difficulty of conferring protection increases, and as soon as the symptoms have appeared only large doses of serum of high immunizing power offer chance of recovery. In rapidly fatal pneumococcus infections, soon after the onset of the symptoms it is no longer possible to rescue the animal. With slower infections cure has been effected when treatment has begun twenty-four hours after the appearance of the first symptoms.

It is well to have clearly in mind the factors which, according to our present knowledge, control the results of this so-called blood-serum therapy. These factors relate to the dose, the immunizing power of the serum used, and the stage and intensity of the disease when treatment is begun. The larger the animal the greater must be the dose, and in the case of tetanus, where the principles of serum therapy have been worked out more fully than for any other disease, the dose is in approximately direct ratio to the weight of the individual. With serum, therefore, of only moderate immunizing power, the quantity required to protect a large animal or man may be so great that its introduction would amount to a transfusion of blood, or might exceed any amount which could be injected. It is of the first importance, therefore, to secure the highest possible degree of immunity in the animal yielding the serum, or else to find some way of obtaining the healing substance in a concentrated form. So far as pneumonia is concerned, neither of these conditions has been fulfilled to an extent analogous to

that for tetanus and diphtheria. In fact we do not possess any such satisfactory experimental basis for the adoption of serum therapy in the treatment of human pneumonia, as we do in the case of tetanus, and it is desirable that laboratory work should supply this basis in the case of an infectious disease, before the general introduction of this principle of treatment for that disease. It is entirely comprehensible from what we know as to the nature of passive immunity and the properties of immune serum, upon which blood-serum therapy depends, that there may be no difficulty in obtaining by this method powerful therapeutic effects in small animals, such as mice and rabbits, and yet we may not be able to attain with the same serum any curative effect in a large animal or man. A person may possess blood and fluids of sufficient immunizing power to protect himself and still not furnish serum of sufficient power to cure another person. It remains yet to be demonstrated by a process such as is successful for tetanus, or by any other process, that animals may be rendered so highly immune from pneumococcus infections as to furnish serum curative for human pneumonia.

Whether or not human beings who have recently recovered from an attack of pneumonia or in other ways have acquired immunity from the pneumococcus may yield serum of sufficiently high immunizing power to exert a curative influence in human pneumonia, cannot at present be positively stated. Some observations indicate that the injection of serum obtained under these circumstances may influence favorably the course of the disease, but it does not appear that any such constant and specific therapeutic effects have been attained as to justify sanguine hopes that by this procedure with its present possibilities the treatment of pneumonia is to be revolutionized.

The immunity in man following an attack of pneumonia appears to be variable both in degree and in duration. How long it may last we cannot say, but repeated attacks of this disease are common. In fact it has been held that one attack increases susceptibility to subsequent attacks. These

facts would suggest that the protection temporarily afforded by a single attack of pneumonia is not due to the production of a very large amount of immunity substance, but we know too little of the real conditions on which immunity from this disease depends and as to the conditions determining duration of immunity to establish such an inference.

The practical difficulties in the way of obtaining, preserving and applying healing serum are sufficiently obvious to require no especial comment. Inasmuch as the blood of pneumonic patients at and soon after the crisis may, as I have found by experiments on rabbits, possess marked toxic properties, the use of such blood serum cannot be said to be free from possibilities of danger.

The future may succeed in surmounting difficulties which are now apparent. With a clearer understanding of the basis of immunity from the pneumococcus means may be found to heighten this immunity. Methods may be discovered by which curative substances may be separated in a more concentrated, permanent and easily handled form, than that in the original serum of immune individuals.

The present outlook for the successful employment of the direct chemical products of bacteria and more particularly of the active vaccinating products, in the treatment of acute infectious diseases is not promising. Inasmuch as it is by such actively immunizing products that immunity is under natural conditions acquired from an infectious disease, and as we have reason to believe that natural recovery consists essentially in the development of this immune condition, it did not seem unreasonable to hope that the injection of such vaccinating bacterial products might exert a curative influence. It was soon observed, however, that the immediate effect of such injection, corresponding to the period of reaction before establishment of immunity, is often distinctly unfavorable and is attended with increased susceptibility to the micro-organism yielding the products.

Whether this unfavorable influence may be checked by further purification of the vaccinating products and removal

of toxic substances is not at present clear. Some experiments, especially with the pneumococcus, seem to indicate such a possibility, but it cannot be said that we have yet succeeded in wholly separating the protective from the toxic properties of bacterial products and it may be that retention of some toxic property is essential for the production of immunity.

A further obstacle to the successful application of these vaccinating substances to the treatment of infections, is that unlike the healing serum they require an interval of time, often of days, before insusceptibility to the disease is manifested and hence they cannot be expected to do any good in rapidly fatal infections. By concentration of the vaccinating fluids this interval may be shortened, and in this way Klemperer has succeeded in curing slow pneumococcus infection of moderate severity in rabbits. At the present moment however, hopes of finding specific curative agents rest in healing serum rather than in cultural bacterial products. We are in the midst of a period of active experimentation revealing new and unexpected facts and points of view concerning this whole subject, and it would be hazardous to pass any verdict at the present moment.

We have now passed in review the more important facts concerning the known morphological and biological properties of the diplococcus pneumoniæ. It now remains to consider the observations relating to the presence and effects of this interesting micro-organism in human beings.

That the diplococcus pneumoniæ is the specific cause of at least the great majority of cases of acute lobar pneumonia is no longer open to dispute. This organism is present regularly and in large number in the pulmonary exudate of this disease, and also in most of the complicating inflammations, such as pleurisy, pericarditis and meningitis. In the majority of cases it is the only bacterial species present. The pathogenic effects obtained by inoculation of its cultures in animals, form an important link in the chain of evidence. The proof is clinched by the demonstration in the bodies of those

affected with or convalescent from croupous pneumonia of specific toxic and immunizing proteids, which, so far as known, can be produced only through the activities of the pneumococcus.

The only point in this connection which can be considered at all unsettled, is whether this organism is the specific cause of all cases of genuine acute lobar pneumonia. The pioneer investigators of this subject, A. Frænkel and Weichselbaum, expressed opposite opinions on this point, Frænkel believing that the pneumococcus is the sole cause of lobar pneumonia, and Weichselbaum contending that it is the most common and important cause, but that in some cases other organisms play the causal role.

The number of competent bacteriologists—and this question is purely a bacteriological one—who hold to Weichselbaum's eclectic view is much smaller now than formerly, and is decreasing with advance in our knowledge of the peculiar properties of the micrococcus lanceolatus.

Failures to find this organism in the affected lung in cases of croupous pneumonia date for the most part from a period in which all of the requirements necessary to establish its absence were not completely understood. Ordinarily there is no particular difficulty in demonstrating the presence of the pneumococcus in croupous pneumonia by microscopical examination, by culture and by inoculation of mice and rabbits with a bit of the hepatized lung. But it may happen that one or two of these procedures give a negative result, when the other succeeds. Therefore when all three methods have not been employed, a negative result of the bacteriological examination is not conclusive. At the time of the examination it may be that most of the cocci are dead or incapable of development in our cultures. This is particularly common in old metapneumonic empyæmas.

From what has already been said regarding the assumption by pneumococci of the form of streptococci, it is probable that some investigators have described under the latter name in cases of croupous pneumonia forms of the pneumococcus.

It is not very uncommon to find associated with the pneumococcus in croupous pneumonia other bacteria, particularly the pyogenic staphylococci and streptococci, and less frequently Friedländer's pneumo-bacillus. The co-existence of these other bacteria, although it may influence the course and character of the disease, cannot of course detract from the etiological primacy of the pneumococcus.

It will be remembered that the micrococcus lanceolatus was first discovered by Sternberg and by Pasteur in the human saliva, and hence it received the name of micrococcus of sputum septicæmia, as the injection of saliva containing virulent lanceolate cocci causes septicæmia in rabbits and mice. The pneumococcus is a frequent inhabitant of the mouth in health, occurring in the virulent state in this situation in fifteen to twenty per cent. of healthy adults. It is even more common in the mouths of those who have recovered from pneumonia. According to Netter it is to be found in sixty-six per cent. of such persons. It is less common in the mouths of children, the estimates varying from five to fifteen per cent.

If we include pneumococci with little or no virulence, the percentage of cases in which it is present in the mouths of healthy persons is much greater. In fact Kruse and Pansini bring good evidence to show that the pneumococcus, or some of its varieties, with or without virulence, is a regular inhabitant of the mouth.

The diplococcus pneumoniæ is present regularly in the expectoration of acute lobar pneumonia, but its presence is deprived of diagnostic value by the facts just stated.

The presence of the pneumococcus in the mouth in health is not an argument against the pathogenic powers of this organism in man. We have several other examples of the frequent presence of undoubtedly infectious bacteria in the mouth, intestinal canal and other exposed situations in the human body in health. Indeed the existence of the pneumococcus in healthy persons is a help, rather than a hindrance,

to our understanding of the etiology of pneumonia. It permits, even compels, us to give due weight to all of the so called predisposing, secondary or accessory causes of this disease, causes often so manifestly operative that they may seem to be, as they were once believed to be, the efficient causes.

Pneumonia is one of those infectious diseases in which predisposition is an important etiological factor. In what way such predisposing or secondary causes as exposure to cold, season, climate, pre-existing disease, alcoholism, old age, injuries to the chest, act in favoring the onset of pneumonia, we do not know. We can imagine that some may enhance the virulence of the pneumococcus, or facilitate its ingress to the deeper air passages, or render the pulmonary tissues less resistant to its invasion and multiplication, or weaken the general insusceptibility of the system. But with our present imperfect knowledge it is not profitable on this occasion to discuss these speculations. Certain diseases, notably measles and perhaps influenza, have been found to be associated with exaltation of virulence of the pneumococci contained in the mouth. We cannot say how often infection resulting in pneumonia is due to pneumococci received from without, as would seem to be the case in some instances of epidemic and contagious pneumonia, or to pneumococci already present in the body.

The distribution of the specific micrococci in cases of croupous pneumonia is subject to considerable variation. In most cases the number of diplococci in the affected part of the lung is large. Living pneumococci are particularly abundant at the margin of an advancing pneumonia, which is evidence that they are not merely secondary settlers in a soil already prepared for them by pre-existing disease. They are often contained within leucocytes.

Pneumococci are generally numerous in the fibrinous pseudo-membrane on the pleura, which accompanies all croupous pneumonias reaching the surface of the lung. They are usually present in the bronchial lymph glands.

In the majority of cases the cocci are not abundant in the circulating blood. The larger the quantity of blood used for inoculating culture media or animals, the greater the chances are of demonstrating the presence of pneumococci. It is probable that in most, if not all, cases a certain number of cocci get into the blood, but it may be in such small number or for such short sojourn that their presence will readily escape detection.

Sometimes the number of cocci found after death in the blood in the heart and vessels is large, exceptionally as large as in pneumococcus septicæmia of the rabbit. Often, although not invariably, this extensive invasion and reproduction of the cocci in the blood corresponds to the so-called asthenic or typhoid pneumonias.

Inasmuch as the pneumococci are not infrequently carried by the circulation in cases of croupous pneumonia, it is not surprising to find them in distant organs, as the spleen, kidneys, liver, joints, bone marrow, brain and meninges. In these situations they may be present without doing demonstrable injury, or they may multiply and cause lesions. It is not rare to find the specific cocci in the intestinal canal, and they may penetrate the bile.

It is a noteworthy fact that the complications of croupous pneumonia, in contradistinction to those of typhoid fever and many other diseases, are, in the majority of instances, referable to the same micro-organism which causes the primary disease. Our consideration of the manifold pathogenic possibilities of this variable organism has prepared us for this fact. Complicating pleurisy, pericarditis, meningitis, peritonitis, endocarditis, nephritis, enteritis, parotitis, arthritis may all be due to special secondary localizations of the pneumococcus. In fact each of these and many other local inflammations may be caused by the same organism, independently of the existence of croupous pneumonia as either a primary or secondary affection.

This general rule as to the etiology of complications of pneumonia is subject to many exceptions. As in typhoid

fever, scarlatina, diphtheria, tuberculosis, pyogenic staphylococci and streptococci, may find the way open in pneumonia for their entrance and multiplication within the body, and these secondary invaders may cause various local inflammations and septicæmia.

The occurrence of abscess of the lung as a complication or sequel of pneumonia is usually the result of secondary infection with pyogenic cocci. In gangrene of course the putrefactive bacilli are present.

It is interesting to consider what lesions are attributable to the actual presence and multiplication of the pneumococci and what to the absorption of soluble chemical products into the general circulation. In all acute exudative inflammations the cocci are present in the exudate. The diffuse fatty and parenchymatous degenerations are due to the absorption of chemical products. There are probably few at the present day who any longer attribute these degenerations in pneumonia to high temperature. There is evidence that swelling of the spleen, which is common, although not constant, in pneumonia is also due rather to the action of absorbed chemical products than to the actual presence of the microorganism in this organ. Focal necrotic lesions of the liver, such as are extremely common in pneumococcus infections of the rabbit, I have occasionally met with in the human liver in pneumonia. I have experimental evidence that the toxic chemical products of the pneumococcus are capable of producing these focal necroses. To the action of the products of the pneumococcus we can attribute the increase of the fibrin factors in the blood, which characterizes many cases of pneumonia.

The decision as to the relative influence of the actual presence of the pneumococcus, or of the action of its absorbed products in causing the renal complications of pneumonia, is not at present altogether clear. Pneumococci are more frequently, in my experience, to be found in the kidneys in cases of croupous pneumonia than in any other extra-thoracic organ. Faulhaber, who has carefully studied this question,

thinks that it is improbable that the purely parenchymatous changes, such as desquamation, cloudy swelling, fatty degeneration and necrosis of epithelium, the hyaline degeneration of vessels and the formation of casts are referable directly to the bacteria. These changes are more probably attributable to bacterial products. On the other hand he considers that the inflammatory alterations, particularly the exudation of white and red corpuscles and of fluids and the interstitial infiltration with small round cells are probably directly dependent upon the presence of bacteria in the kidney. Inasmuch, however, as it is possible to produce experimentally by the chemical products the enumerated inflammatory changes, there is no strict proof that these also may not be due to bacterial toxic products. In other words, I think it probable that all of the lesions of an acute diffuse nephritis may be caused by toxic substances, without the necessary presence of bacteria.

Pneumococci have been found only exceptionally in the urine of pneumonic patients.

It has been shown by experiments upon animals that the injection of bacteria or their products into the circulation causes primarily a diminution in the number of leucocytes in the circulating blood. In rapidly fatal infections this diminution is often extreme, and may continue until death. If recovery takes place there is an increase in leucocytes, often considerably beyond the normal. In infections of protracted course there is no general law, often a notable oscillation in the number of leucocytes being observed within short intervals. If the infection is characterized by local inflammatory exudation, there is leucocytosis, proportionate within limits to the extent and character of the inflammation. This leucocytosis is attributed to the absorption by the blood of positively chemotactic substances, such as we know to be frequently formed by bacteria, but it cannot be said that this explanation of leucocytosis is proven beyond question. In accordance with these experimental observations we find that leucocytosis, in greater or less degree, is commonly

present in pneumonia. The absence or disappearance of leucocytosis in this disease is an unfavorable prognostic sign.

The pneumococcus has been demonstrated to be the specific cause of all the varying types of genuine acute lobar pneumonia, the sthenic, the asthenic, the bilious, the typhoid, the alcoholic, the epidemic, etc.

We owe to Jürgensen the distinction between primarily and secondarily asthenic pneumonias. So far as the secondarily asthenic pneumonias are concerned, that is, pneumonias which assume an asthenic type as the result of alcoholism, old age, pre-existing disease or other debilitating influences, it is not necessary to assume any increased virulence on the part of the infecting pneumococci. The greater gravity of the symptoms can be explained by the lessened resistance of the system to the pneumococcus and its poisons.

There is more reason to assume more than ordinary virulence on the part of the pneumococci in primarily asthenic pneumonias, especially in times and places where nearly all who are attacked, including the previously vigorous, acquire the asthenic type. The extraordinary variability in the degree of virulence manifested by the different varieties of the diplococcus pneumoniæ renders this view permissible. Nevertheless, even under these conditions, it is possible that the asthenic type is due to influences, which, acting perhaps upon many persons in a household or community, weaken resistance to the pneumococcus.

Although enlightened physicians have often recognized that the gravity of acute lobar pneumonia cannot be measured by the extent of the pulmonary inflammation, nevertheless it is not uncommon to find writers even at the present day who attribute the principal dangers of the disease to such elements as hyperæmia of the lungs, accumulation of inflammatory products, obstacles to the pulmonary circulation, removal of lung surface from the respiratory function. Indications for treatment are sometimes based chiefly upon this mechanical conception of the disease.

The degree and extent of the pulmonary inflammation afford an index of the severity of the disease much in the same way as high temperature does. They are not the real dangers in the majority of cases, although they are of course not to be ignored as sometimes the direct cause of grave symptoms, and as affording indications for treatment. Both clinical experience and the bacteriological study of this disease support the view that in the majority of cases the grave constitutional manifestations of lobar pneumonia are due to toxic substances circulating in the blood and acting injuriously on the respiratory centres and other parts of the nervous system, on the heart, the kidneys and other parts.

There are indeed reasons which lead us to think that local inflammatory exudations in infectious diseases may subserve a useful, conservative, protective purpose. We cannot regard the inflammatory exudate in pneumonia as *per se* a good thing, but it may be the most desirable occurrence possible under the circumstances of the invasion of virulent pneumococci into the lungs of susceptible persons. Experiments upon animals show that it is just those infections with the pneumococcus which are unattended by marked inflammation at the point of entrance which run a rapidly fatal course, and that there is often a direct relation between the development of local inflammation and the severity of the disease in the sense indicated.

Even if it were within our power to arrest the hyperæmia and exudation of leucocytes and other products of inflammation, we should confer a very doubtful benefit upon the patient, unless at the same time we injured the bacteria. It is very likely that in so doing we should rob nature of a weapon which she is using as efficaciously as possible against these invading micro-organisms. It is doubtless often a fortunate thing for the patient that it is not within the power of the physician to accomplish what he considers to be indicated in the way of treatment.